REMARKS/ARGUMENTS

Status of the Application:

At the time the Office Action was mailed, Claims 54 and 55 were pending in the application. All rejections in the previous office action (Paper No. 14) were withdrawn in view of Applicants' amendments and arguments in Paper No. 18. Applicants' election without traverse of Group IIv was acknowledged. The Office Action newly rejected Claims 54 and 55 under 35 U.S.C. § 102(b). This Reply is accompanied by a Request for Continued Examination along with the appropriate statutory fee.

In this Reply, Applicants have cancelled Claims 54 and 55 and added new Claims 56-58. No new matter has been added. Therefore, upon entry of this amendment, Claims 56-58 will be before the Examiner for consideration.

Rejection Under 35 U.S.C. § 102:

Former Claims 54 and 55 were rejected under 35 U.S.C. § 102(b) as being anticipated by Danik et al., 1991 ("Danik"). According to the Office Action:

> Danik et al. teach a cDNA library from a human glioma (pg. 8578, 1st col.), which is a collection of expressed gene transcripts from a plurality of cells that are the progeny of a single glioma tumor cell, by definition, and as claimed.

Claim 56 introduced herein recites "a cDNA library produced from a glioma tumor stem or progenitor cell, said library comprising cDNAs encoding at least one marker of neuronal lineage and at least one marker of glial lineage." Support for this claim is found in the specification, for example, on p. 47, lines 10-15. As described in this passage, the data shows that "primitive stem or progenitor cells of the human brain can be associated with glioma neoplastic transformation."

Claim 57 dependent on Claim 56 recites particular markers of neuronal lineage, including "beta-III tubulin, neuron-specific enolase, neurofilament M, tenascin and MAP2," and recites particular markers of glial lineage, including "glial fibrillary acidic protein and nestin." Support for the presence of these transcripts in human glioma microclones (the source of the mRNA for the claimed cDNA libraries) is found in the specification (p. 47, lines 10, 11): "[p]opulations [of microclones] from different primary gliomas showed individual profiles of gene expression similar to those of normal human brain stem and progenitor cells." A listing of particular transcripts expressed by normal human brain stem and progenitor cells is shown in Table 3, on p. 43. The individual transcripts are further identified as markers of neuronal, or of glial, lineage, on p. 43, lines 19-27.

In contrast to the claimed invention, Danik does not disclose or suggest a cDNA library produced from a glioma tumor stem or progenitor cell. The source of the cDNAs in Danik is simply described as "human glioma" (Danik p. 8578, lines 5,6) or "human malignant astrocytoma" (Danik p. 8580, Discussion, line 3). Furthermore, Danik does not disclose or suggest the claimed cDNA library "comprising cDNAs encoding at least one marker of neuronal lineage and at least one marker of glial lineage." In fact, Danik discloses only one transcript from a cDNA library, i.e., a "marker of cell death" termed pTB16 (see Danik title and abstract).

The Office Action states that "a cDNA library from a human glioma ...is a collection of expressed gene transcripts from a plurality of cells that are the progeny of a single glioma tumor cell, by definition." The Advisory Action notes that "gene transcripts isolated from a glioma are reasonably the same, no matter if they are isolated

from a microclone or not...absent evidence to the contrary." Applicants respectfully point out that their specification provides abundant evidence that is contrary to this assertion. First, it is noted that the specific collection of transcripts expressed in a tumor will differ depending upon the stage of the tumor (specification, p. 47, lines 7-9):

> [t]he dedifferentiation dysembryoplastic development of any cell cloned is a continuum as genes are turned on and off, distinguishing stages of that cell's development. Thus, tumors can be defined by their genetic profile rather than their phenotype or microscopic profile.

Second, it is directly demonstrated in the instant specification (Example 6, § 5.6.0, p. 46, line 19- p. 47, line 15) that microclones derived from tumor cells at various stages display temporal ordering of gene expression as a function of the tumor stage. Therefore, in contrast to the Examiner's assertion, gene transcripts isolated from a glioma are *not* reasonably the same, no matter if they are isolated from a microclone or not. In fact, they are not reasonably the same either if they are isolated from gliomas at different stages of tumorigenesis, or if they are isolated from microclones derived from gliomas at different stages.

Finally, cDNAs encoding at least one marker of neuronal lineage and at least one marker of glial lineage would not be inherent in the cDNA library of Danik absent evidence that the astrocytoma tumor used in Danik was at a stage in which stem or progenitor cells producing such transcripts could have been present. Danik is completely silent on this point. Furthermore, Applicants were able to produce their cDNA libraries from tumor stem/progenitor cells only by using specialized culture techniques and media necessary for maintaining and propagating microclones derived from tumor stem/progenitor cells *in vitro*. These methods were not known at the time of publication

of Danik (i.e., 1991). (See specification, at p. 12, lines 5-16, for the definition of "microclone" as an "isolated system that can be created from a variety of cell types in which all of the cells in the microclone are the progeny of a single primogenitor or ancestor cell," and p. 12, lines 15-16, as well as Example 6, pp. 46, 47, describing creation of microclones by cultivating a single progenitor cell under specified conditions in culture.)

Claim 57 recites independently patentable subject matter. Claim 57 recites particular markers of neuronal lineage ("beta-III tubulin, neuron-specific enolase, neurofilament M, tenascin, and MAP2"), and particular markers of glial lineage ("glial fibrillary acidic protein and nestin"). None of the claimed markers is disclosed in the cited art.

Conclusion:

Because the cDNA library of Danik does not disclose or inherently contain cDNAs encoding at least one marker of neuronal lineage and at least one marker of glial lineage, Claim 56 and claims dependent thereon are patentable claims.

Applicants have made every effort to present claims which distinguish over the cited art, and believe that all claims as presented herein are now in condition for allowance. However, Applicants invite the Examiner to call the undersigned if it is believed that a telephonic interview would expedite the prosecution of the case to an allowance.

This response is filed with a petition for a two month retroactive extension of time and the required fee. The Commissioner is hereby authorized to charge any

underpayment or credit any overpayment of fees under 37 C.F.R. 1.16 or 1.17 as required by this paper to Deposit Account 50-0951.

Respectfully submitted,

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